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VR2001A000031 12 March 2001 (12.03.2001) IT

(71) Applicant *(for all designated States except US)*: CONSORZIO PER GLI STUDI UNIVERSITARI [IT/IT]; Via dell'Artigliere, 8, I-37129 Verona (IT).

(71) Applicant and
(72) Inventor: SUZUKI, Hisanori [IT/IT]; Via Memeli, 43, I-37126 Verona (IT).

(74) Agent: SANDRI, Sandro; Europatent - Euromark S.r.l., Via Locatelli, 20, I-37122 Verona (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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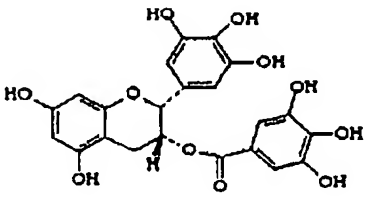
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/072086 A2

(54) Title: USE OF EPIGALLOCATECHIN-3-GALLATE OR ITS DERIVATIVES IN THE PREVENTION AND TREATMENT OF NEURODEGENERATIVE DISEASES



(I)

(57) Abstract: An epigallocatechni-3-gallate compound with the following formula (I), or its derivatives, is used for the prevention and treatment of neurodegenerative diseases, like for example of Parkinson's disease, Alzheimer's disease, Creutzfeld-Jacob syndrome, sleeping sickness caused by protozoa, including Trypanosoma brucei rhodensiense and Trypanosoma brucei gambiense, as well as for the treatment of asthma, diabetes, cardiovascular diseases, obesity.

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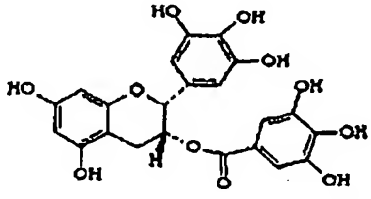


(I)

(57) Abstract: An epigallocatechni-3-gallate compound with the following formula (I), or its derivatives, is used for the prevention and treatment of neurodegenerative diseases, like for example of Parkinson's disease, Alzheimer's disease, Creutzfeld-Jacob syndrome, sleeping sickness caused by protozoa, including Trypanosoma brucei rhodensiense and Trypanosoma brucei gambiense, as well as for the treatment of asthma, diabetes, cardiovascular diseases, obesity.

USE OF EPOGALLOCATECHIN-3-GALLATE OR DERIVATIVES THEREOF IN THE PROPHYLAXIS AND TREATMENT OF NEURODEGENERATIVE DISEASES

****

TECHNICAL FIELD

The present invention relates to the use of a compound or its derivatives in the prevention and treatment of neurodegenerative diseases.

Neurodegenerative diseases are a significant problem at a socio-economic and health level. Reference may be made to Parkinson's disease and Alzheimer's disease, which are the main causes of dementia in the population of America and Europe, Creutzfeldt-Jacob syndrome caused by prion, and sleeping sickness caused by protozoa, including Trypanosoma brucei rhodensiense and Trypanosoma brucei gambiense. Sleeping sickness is one of the main causes of death in the African population.

The drugs currently available for the treatment of neurodegenerative diseases do not allow effective therapies and, therefore, the pharmacological treatment of these diseases is unsatisfactory.

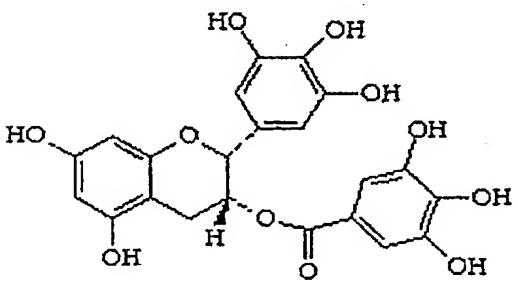
Neurodegenerative disease are caused by the death of nerve cells, for example astrocytes, astroglia and neurons. These nerve cell degenerative processes are linked to the action of interferon-γ (IFN-γ) (Galimberti D. et al. (1999) Biochem. Biophys. Res. Comm. 263, 251-256; Hunot S. et al. (1999) J. Neurosci. 19 3440-3447; Blasko I. et al. (1999) FAsEB J. 13 63-68; Suo Z. et al. (1998) Brain Res. 807 110-117; Delgado et al.(1998) J. Leukoc. Biol. 63 740-745; Rossi F, Bianchini E. (1996) Biochem. Biophys. Res. Co-un. 225 474-478; MedaL. et al (1995) Nature 374, 647-

650) which, by activating a nuclear factor STAT1 (Signal transducers and activators of transcription 1), carries out the various pleiotropic actions (Boehm, U. et al.(1997) Annu. Rev. Immunol. 15, 749-795; Kordula T. et al. (1998) J. Biol. Chem. 273 4112-4118; Kitamura Y. et al Neurosci. Lett. 237 17-20). Amongst the various actions of interferon-γ in the cell, of particular importance is its ability to modulate the expression of an enzyme, inducible nitric oxide synthase (iNOS), which by producing large quantities of NO can kill off nerve cells. This explains why interferon-γ is a cause of the onset of neurodegenerative diseases.

The need was felt for the availability of drugs for the prevention and treatment of neurodegenerative diseases, which would be particularly effective in inhibiting the activation of STAT1.

This technical problem was solved by using the compound epigallocatechin-3-gallate, or its derivatives.

As a result, the present invention also relates to the use of compounds with the following formula (I), or its derivatives in the prevention and treatment of neurodegenerative diseases:



(I)

The activity of compounds with the formula (I) in neurodegenerative diseases was demonstrated in the present invention by means of an experimental in vitro model, using U251 human glioblastoma cells. In this experiment it was demonstrated that, for example using epigallocatechin-3-gallate (EGCG) as the invention compound, in a concentration of 5 μM, the invention compounds are effective in the treatment of neurodegenerative diseases, inhibiting 50% of the maximal activation of STAT1 induced by interferon-γ.

The compounds according to the present invention are normally used in the in vitro experiments (see the examples) in doses of between 1 and 50 μM, preferably from 5 to 20 μM, in a DME culture, complete with 10% v/v of fetal bovine serum.

The Applicant found that STAT1 inhibition normally occurs in a dose-dependent manner.

The inhibitory action of the compounds according to the present invention in the neurodegenerative processes described above is not attributable to the anti-oxidant, anti-inflammatory or anti-tumor activity of the compounds with formula (I). Effectively, using U251 human glioblastoma cells it was demonstrated that anti-oxidant, anti-inflammatory or anti-tumor drugs cannot inhibit activation of STAT1 induced by interferon-γ (see the examples). Vitamin C was used as the anti-oxidant. This compound was not active even at a dose of 100 μM. The anti-inflammatory compound used was hydrocortisone, a steroidal anti-inflammatory drug. This compound was also inactive, even

at a dose of 100 μM. The non-steroidal anti-inflammatory drug Ibuprofen was used, and was not active at a dose of 400 μM. The anti-tumor compound used was cisplatin, which was not active at a dose of 17 μM.

The Applicant demonstrated that in order to inhibit STAT1 activity, the structure of the compounds with formula (I) is specific: neither gallic acid nor epigallocatechin, which are the two polyphenolic components of EGCG, have a STAT1 inhibitory action.

Epigallocatechin-3-gallate is available on the market. It is the main ingredient of green tea extract. The methods for its isolation are indicated in Merck Index Edition 12 in the above-mentioned literature.

Pharmaceutical formulations containing the compounds according to the present invention contain the usual vehicles and excipients. They may be in the form of tablets, capsules or in formulations suitable for parenteral administration.

Effective doses of the compounds according to the present invention are those typically used in clinical medicine for epigallocatechin-3-gallate, or lower.

Pharmaceutical formulations containing the compounds according to the present invention can be prepared using techniques well known to experts in the field. See, for example, "Remington's Pharmaceutical Sciences 15th Ed."

Activation of the STAT1 system also plays an important part in other diseases, such as asthma (Guo F.H. et al. J. Immunol. 2000, 164(11) 6970-80; Sampath e al., J. Clin. Invest. 1999, 103(9) 1353-61), diabetes (Hill N.J. et al., Diabetes 2000 49(10) 1744-7; Sekine N. et al. J.

Cell Physiol. 2000 184(1) 46-57), cardiovascular diseases (J. Biol. Chem. 2000 275 10002-8), obesity (Scarpace P.J et al., Neuropharmacology 2000, 39(10) 1872-9; Velloso L.A. et al. Cardiovasc. Res. 1998 272(26) 16216-23). The products according to the present invention can also be used to treat these diseases.

The following examples illustrate the present invention without limiting the scope of application.

EXAMPLE 1

The cell line of U251 human glioblastoma was cultivated, at 37°C, in a DMEM 12-614 (Dulbecco's modified eagle medium BioWhittaker Co.) culture complete with 10% of fetal bovine serum. The serum was eliminated 4 hours before treatment with interferon-γ (250 U/ml). The epigallocatechin gallate concentration (R = H, indicated as EGCG) used was 1 μM in the DMEM culture.

STAT1 activation was measured by means of EMSA (electrophoretic mobility shift assay). 10 tg of nuclear extract (Osborn, L., Kunkel, S., and Nabel, G.J. (1989) *Proc. Natl. Acad. Sci. USA* 86, 2336-2340) were incubated at room temperature for 20 minutes with [^{32}P]- double-stranded oligonucleotide (5'-gtegaCATTTCCCCGTAAATCg-3') (Wagner, B.J., Hayes, T.E.f Hoban, C.J., and Cochran, B.H. (1990) *EMBO* J. 9, 4477-4484). The products were fractionated by means of electrophoresis on non-denaturing polyacrylamide gel. The intensity of the delayed bands was measured using the Phosphorimager system (Molecular Dynamics, Sunnyvale, CA, USA).

The results are indicated in example 27.

EXAMPLE 2

Example 1 was repeated, but with a concentration of

2 μM in the DMEM culture.

The results are indicated in example 27.

EXAMPLE 3

Example 1 was repeated, but with a concentration of 5 μM in the DMEM culture.

The results are indicated in example 27.

EXAMPLE 4

Example 1 was repeated, but with a concentration of 10 μM in the DMEM culture.

The results are indicated in example 27.

EXAMPLE 5

Example 1 was repeated, but with a concentration of 20 μM in the DMEM culture.

The results are indicated in example 27.

EXAMPLE 6

Example 1 was repeated, but with a concentration of 50 μM in the DMEM culture.

The results are indicated in example 27.

EXAMPLES 7-10 comparison with an anti-oxidant compound

In these examples vitamin C was used as an anti-oxidant compound for comparison, in concentrations of 10 μM, 20 μM, 50 μM and 100 μM in the DME culture.

The results are indicated in example 27.

EXAMPLES 11-14

Comparison with a steroidal anti-inflammatory compound

In these examples hydrocortisone was used as a steroidal anti-inflammatory compound for comparison, in concentrations of 10 μM, 20 μM, 50 μM and 100 μM in the DMEM culture.

The results are indicated in example 27.

EXAMPLES 15-19

Comparison with a non-steroidal anti-inflammatory compound

In these examples ibuprofen was used as a non-steroidal anti-inflammatory compound for comparison, in concentrations of 10 μM, 50 μM, 100 μM, 200 μM and 400 μM in the DMEM culture.

The results are indicated in example 27.

EXAMPLES 20-23

Comparison with an anti-tumor compound

In these examples cisplatin was used as an anti-tumor compound for comparison, in μM concentrations in the DMEM culture.

The results are indicated in example 27.

EXAMPLE 24 Comparison

Examples 1 to 6 were repeated, but using epigallocatechin as the active compound in place of EGCG. Epigallocatechin is one of the two polyphenolic components of EGCG. The results are indicated in example 27.

EXAMPLE 25 Comparison

Examples 1 to 6 were repeated, but using gallic acid as the active compound in place of EGCG. Gallic acid is the second polyphenolic compound of EGCG. The results are indicated in example 27.

EXAMPLE 26 Comparison

Example 1 was repeated, but using Interleukin 6 (IL-6) instead of IFN-1 as the STAT1 activator. Interleukin 6 is a known STAT3 activator. HeLa human cell lines (human cervical tumor cells) were also used; or HepG2 human liver tumor cell lines; or MCF7 human breast tumor cell lines.

The compound to be tested was EGCG (50 μM), the com-

pound with formula (I) according to the present invention.

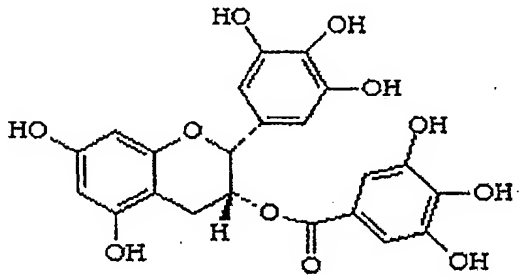
EXAMPLE 27 Results

IFN-γ rapidly induces strong STAT1 activation in the U251 human glioblastoma cell line.

All of the compounds according to the present invention and those used for comparisons are added to the U251 cell culture half an hour before treatment with IFN-γ.

CLAIMS

1. A use, for the prevention and treatment of neurodegenerative diseases, of an epigallocatechin-3-gallate compound with the following formula (I), or its derivatives:



(I)

2. A use according to claim 1, in the prevention and specific treatment of Parkinson's disease, Alzheimer's disease, Creutzfeldt-Jacob syndrome, sleeping sickness caused by protozoa, including Trypanosoma brucei rhodensiense and Trypanosoma brucei gambiense.

3. A use according to claim 1, in the prevention and specific treatment of asthma, diabetes, cardiovascular diseases, obesity.

4. A use according to any of the foregoing claims, for the inhibition of STAT1 (Signal transducers and activators of transcription 1) maximal activation induced by interferon-γ.

5. A use according to any of the foregoing claims, in which the compound is produced in the form of tablets, capsules or in formulations suitable for parenteral administration.

6. A use according to any of the foregoing claims, in which the effective doses of the above-mentioned compound are those typically used in clinical medicine for epigallocatechin-3-gallate, or lower.

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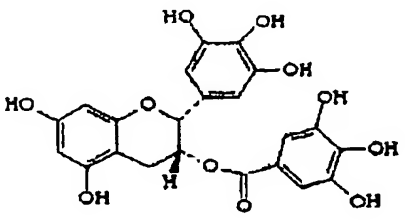

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEE, S.-R. ET AL.: "Protective effects of the green tea polyphenol (-)-epigallocatechin gallate against hippocampal neuronal damage after transient global ischemia in gerbils" NEUROSCIENCE LETTERS, vol. 287, no. 3, 30 June 2000 (2000-06-30), pages 191-194, XP002201223 abstract page 192, paragraphs 1,2 ---	1,2,4-6
X	WO 00 06171 A (HME ENTERPRISES LLC ;DYKE KNOX VAN (US)) 10 February 2000 (2000-02-10) page 1, line 20-25 page 23, line 7 -page 24, line 29; claims 1,2,18,22 --- -/--	1,2,4-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2002	02. 10. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beyss, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 02/00149

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 922 756 A (CHAN MARION MAN-YING) 13 July 1999 (1999-07-13) claims 1,2	1,3-6
X	US 5 318 986 A (HARA YUKIHIKO ET AL) 7 June 1994 (1994-06-07) claims 1-3	1,3-6
X	US 5 605 929 A (LIANG TEHMING ET AL) 25 February 1997 (1997-02-25) claims 1,3	1,3-6
X	WO 99 22728 A (ARCH DEV CORP ;LIAO SHUTSUNG (US); HIIPAKKA RICHARD A (US)) 14 May 1999 (1999-05-14) claims 1,6,10	1,3-6
X	DE 196 27 344 A (VITASYN GMBH ENTWICKLUNG & VER) 8 January 1998 (1998-01-08) page 3, line 60,61; claim 1	1,3-6
P,X	WO 01 49285 A (KURPPA LASSE ;SLK FOUNDATION (PA)) 12 July 2001 (2001-07-12) claims 1,6,9,10	1,3-6

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IT 02/00149

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 2, 4-6 (all in part)

   The use of epigallocatechin-3-gallate for the prevention and treatment of neurodegenerative diseases

2. Claims: 1, 2, 4-6 (all in part)

   The use of epigallocatechin-3-gallate for the prevention and treatment of sleeping sickness

3. Claims: 3-6 (in part)

   The use of epigallocatechin-3-gallate for the prevention and treatment of asthma

4. Claims: 3-6 (in part)

   The use of epigallocatechin-3-gallate for the prevention and treatment of diabetes

5. Claims: 3-6 (in part)

   The use of epigallocatechin-3-gallate for the prevention and treatment of cardiovascular diseases

6. Claims: 3-6 (in part)

   The use of epigallocatechin-3-gallate for the prevention and treatment of obesity

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